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Letter to the Editor

Xenopus *chordin* and Drosophila *short gastrulation* Genes Encode Homologous Proteins Functioning in Dorsal-Ventral Axis Formation

Recently published papers by two laboratories report the cloning of genes in Xenopus and Drosophila serving similar functions in establishing the dorsal–ventral axis: Sasai et al. (1994) describe the isolation of Xenopus *chordin*, which encodes a potent dorsalizing factor produced by the Spemann's organizer, and François et al. (1994) report the cloning of the Drosophila *short gastrulation* (*sog*) gene, which is produced in lateral blastoderm cells and antagonizes the action of *decapentaplegic* (*dpp* in dorsal cells, thereby exerting a ventralizing influence. Sequence comparison indicates that *chordin* and *sog* are likely to encode homologous proteins (Figure 1). These two proteins share distributed sequence similarity (27% identity over 941 amino acids; Figure 1A) and four repeats of a motif defined by the spacing of 10 cysteine residues (Figure 1B). The four cysteine repeats in *chordin* are most similar to their counterparts in sog (e.g., 47% amino acid identity between the CR1 repeats) and are present in the same relative positions in the two proteins (Figure 1A).

It is noteworthy that *sog* behaves genetically as an antagonist of signaling via the dpp pathway in Drosophila

Figure 1. Alignment of the Drosophila Sog and Xenopus Chordin Protein Sequences

(A) Alignment of the complete protein sequences. Vertical lines indicate amino acid identities, double dots indicate most conservative amino acid substitutions, and single dots indicate moderately conservative amino acid substitutions. TM (overlined) indicates the location of the single hydrophobic region in the sog protein, which is located in virtually the same position as the signal peptide (SP) of chordin relative to the remainder of the protein. The likely functional equivalence of the standard signal peptide in chordin and the type II membrane-spanning domain in sog are consistent with data indicating type II membrane-spanning domains can function as secretory signals (Shaw et al., 1988). The four copies of the cysteine motifs (CR1–CR4) are double underlined. These CR repeats are aligned to obtain a general CR consensus sequence in (B).

(B) Alignment of the CR repeats of sog and chordin. Boxed residues indicate identities between the corresponding sog and chordin repeats. Bold residues conform to the consensus sequence for CR repeats described below. Stars indicate the location of the cysteine residues in CR repeats that can be aligned according to the consensus $Cx_{24}Cx_2Cx_1Cx_{6-8}Cx_4Cx_4Cx_{12}CCx_2Cx_3R/K$. Single dots denote gaps in the sequence introduced to preserve alignment. A consensus for the cysteine repeats is shown below the aligned sequences. Cysteine residues and one tryptophan residue shared by all repeats are boxed; capital letters in the consensus indicate six or more identities at that position; lowercase letters indicate that three or more repeats contain an amino acid or a similar amino acid using the stringent substitution criteria R or K, E or D, S or T, L or V, L or I, and Q or N; and dashes indicate positions in the consensus where no clear residue is favored. The sog and chordin CR repeats are distantly related to domains present in procollagen, thrombospondin, von Willebrand factor, laminins, and members of the CEF-10 family of proteins as described in François et al. (1994) and in Sasai et al. (1994). The GenBank accession number for *chordin* is L35764 and for *sog* is U18774.

(Ferguson and Anderson, 1992; Wharton et al., 1993; François et al., 1994) and that the nonautonomous dorsalizing effect of chordin on dorsal–ventral axis formation (Sasai et al., 1994) is opposite to that of BMP-4 (a dpp paralog) in Xenopus (Graff et al., 1994). In Drosophila, dpp is required for the formation of dorsal structures, and vertebrate BMP-4 can substitute for this function (Padgett et al., 1993). In vertebrates, BMP-4 is likely to be required for the formation of ventral structures (Dale et al., 1992; Jones et al., 1992; Graff et al., 1994; Suzuki et al., 1994; Maeno et al., 1994; Schmidt et al., 1995) and for bone morphogenesis (reviewed by Kingsley, 1994). Drosophila dpp also functions in the latter assay (Sampath et al., 1993). It is also interesting that the expression domains of *sog* and *dpp* in Drosophila and those of *chordin* and *BMP-4* in Xenopus are complementary. Thus, *sog* is expressed in a broad lateral domain of the Drosophila blastoderm embryo abutting the dorsal domain of *dpp* expression (François et al., 1994), and *chordin* is expressed dorsally in early Xenopus embryos (Sasai et al., 1994) in a pattern reciprocal to that of *BMP-4* in lateral and ventral cells (Fainsod et al., 1994; Schmidt et al., 1995). As there has been speculation that the dorsal–ventral axes in vertebrates and invertebrates have been inverted during evolution (Arendt and Nüblerjung, 1994; Nüblerjung and Arendt, 1994), it is possible that important mechanisms for patterning the dorsal–ventral axis have been conserved following the ancient divergence of vertebrates and invertebrates (i.e., that homologous signaling pathways activate homologous downstream responses). A key question for future investigation is whether chordin and sog function by neutralizing BMP-4 and dpp signaling or whether these molecules function as ligands to trigger distinct antagonistic signaling pathways.

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